

= SOLID SUPPORT

R = TERMINAL PROTECTING GROUP FOR EXAMPLE: DIMETHOXYTRITYL (DMT)

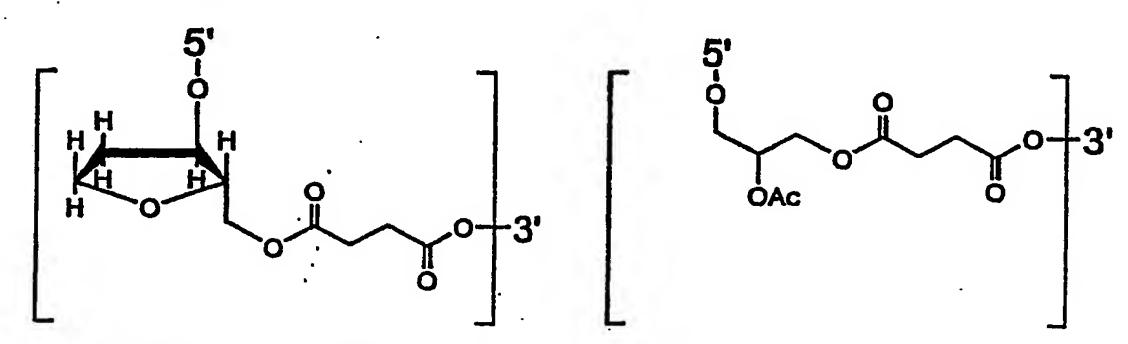
= CLEAVABLE LINKER

(FOR EXAMPLE: NUCLEOTIDE SUCCINATE OR

(NVERTED DEOXYABASIC SUCCINATE)

= CLEAVABLE LINKER

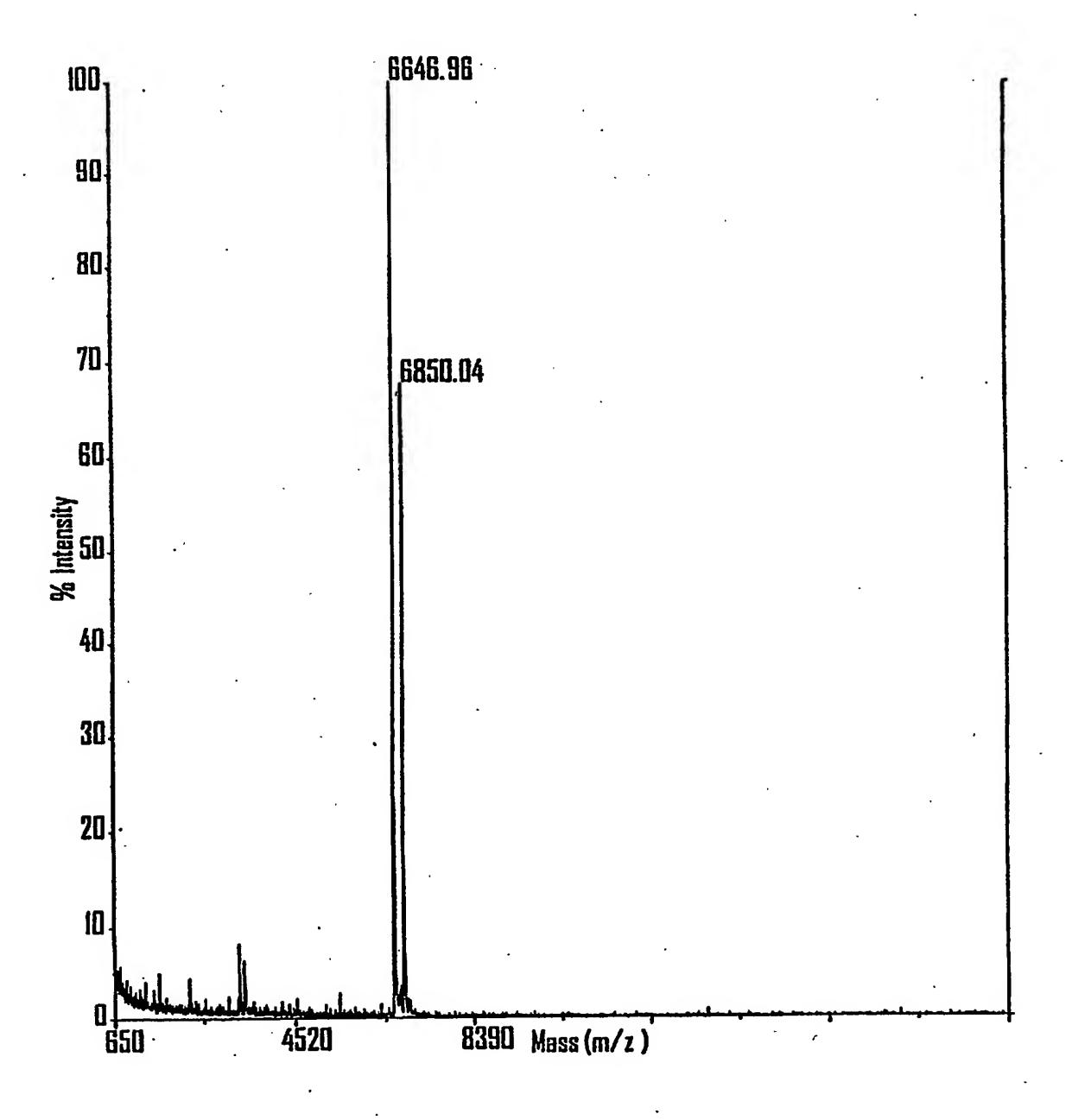
(FOR EXAMPLE: NUCLEOTIDE SUCCINATE OR INVERTED DEOXYABASIC SUCCINATE)

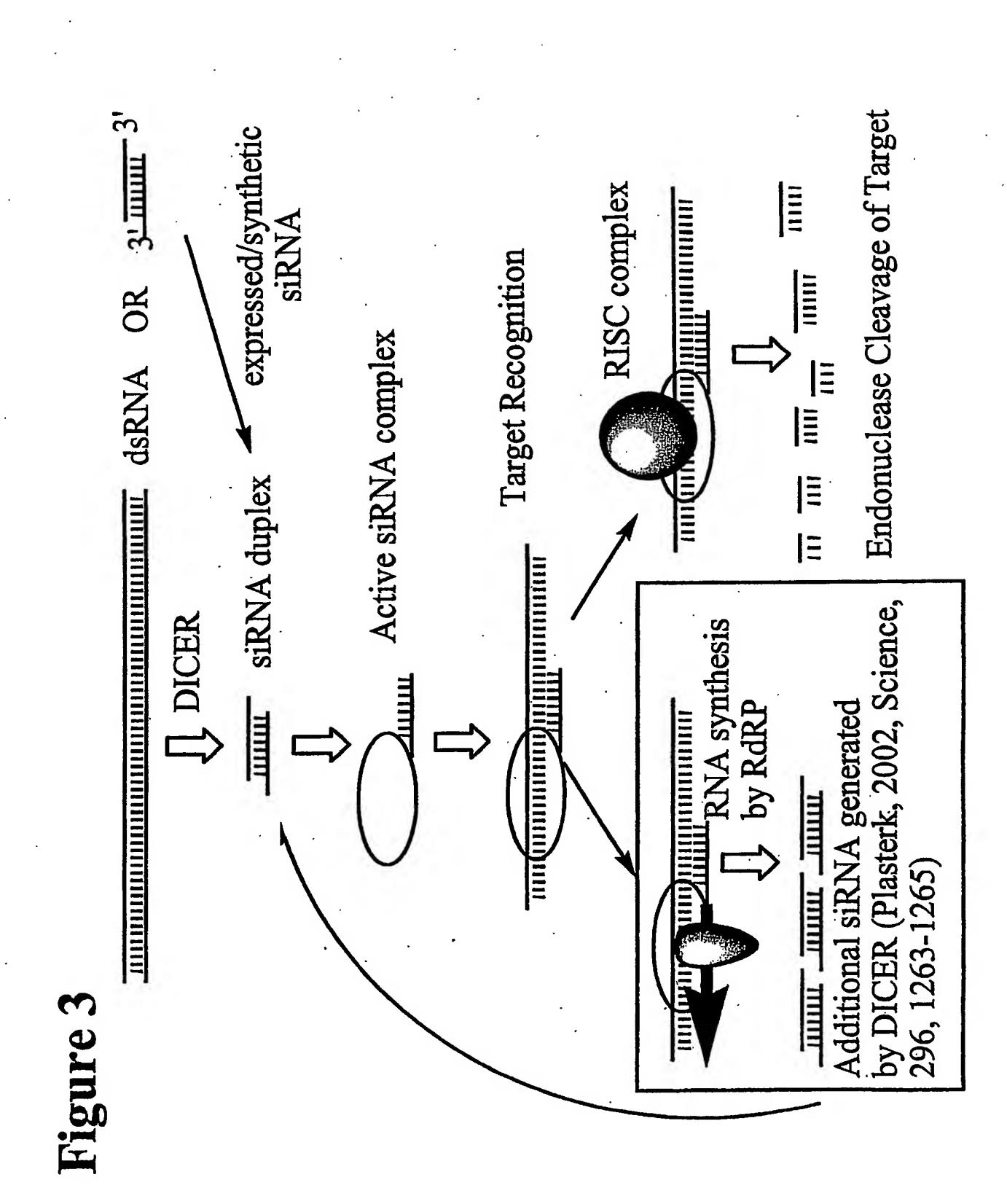


· INVERTED DEOXYABASIC SUCCINATE LINKAGE

GLYCERYL SUCCINATE LINKAGE

Figure 2





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SENSE STRAND (SEQ ID NO 789) ALL POSITIONS RIBONUCLEOTIDE EXCEPT POSITIONS (N N) -3' B-NNNNNNNNNNNNNNNNNNNNNNN-B L-(N_sN) NNNNNNNNNNNNNNNNNNN -5' ANTISENSE STRAND (SEQ ID NO 790 ALL POSITIONS RIBONUCLEOTIDE EXCEPT POSITIONS (N N) SENSE STRAND (SEQ ID NO 791) ALL PYRIMIDINES = 2'-FLUORO AND ALL PURINES = 2'-OM EXCEPT POSITIONS (N N) 5'- $NNNNNNNNNNNNNNNNNNN(N_sN)$ -3' B L-(N_sN) NNNNNNNNNNNNNNNNNNN -5' ANTISENSE STRAND (SEQ ID NO 792) ALL PYRIMIDINES = 2'-FLUORO AND ALL PURINES = 2'-O-ME EXCEPT POSITIONS (N N) SENSE STRAND (SEQ ID NO 793) ALL PYRIMIDINES = 2'-O-ME OR 2'-FLUORO EXCEPT POSITIONS (N N) -3' B-N N N N N N N N N N N N N N N N N N (N N)-B -51 ANTISENSE STRAND (SEQ ID NO 794) ALL PYRIMIDINES = 2'-FLUORO EXCEPT POSITIONS (N N) SENSE STRAND (SEQ ID NO 795)
ALL PYRIMIDINES = 2'-FLUORO EXCEPT POSITIONS (N N) AND ALL PURINES = 2'-DEOXY -31 -5' ANTISENSE STRAND (SEQ ID NO 792) ALL PYRIMIDINES = 2'-FLUORO AND ALL PURÎNES = 2'-O-ME EXCEPT POSITIONS (N N) SENSE STRAND (SEQ ID NO 796) ALL PYRIMIDINES = 2'-FLUORO EXCEPT POSITIONS (N N) 5'-B-NNNNNNNNNNNNNNNNNNNNNNNNN-B E -5' L-(N_sN) NNNNNNNNNNNNNNNNNN ANTISENSE STRAND (SEQ ID NO 792)
ALL PYRIMIDINES = 2'-FLUORO AND ALL PURINES = 2'-O-ME EXCEPT POSITIONS (N N) SENSE STRAND (SEQ ID NO 795)
ALL PYRIMIDINES = 2'-FLUORO EXCEPT POSITIONS (N N) AND ALL PURINES = 2'-DEOXY -3' B-N'NNNNNNNNNNNNNNNNNNNNNN-B F L-(N₅N) N N N N N N N N N N N N N N N N N N -5' ANTISENSE STRAND (SEQ ID NO 797) ALL PYRIMIDINES = 2'-FLUORO EXCEPT POSITIONS (N N) AND ALL PURINES = 2'-DEOXY

POSITIONS (NN) CAN COMPRISE ANY NUCLEOTIDE, SUCH AS DEOXYNUCLEOTIDES (eg. THYMIDINE) OR UNIVERSAL BASES

B = ABASIC, INVERTED ABASIC, INVERTED NUCLEOTIDE OR OTHER TERMINAL CAP THAT IS OPTIONALLY PRESENT

L = GLYCERYL or B THAT IS OPTIONALLY PRESENT

S = PHOSPHOROTHIOATE OR PHOSPHORODITHIOATE that is optionally absent

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		SENSE STRAND (SEQ ID NO 798)	
A	5'-	B-AUGACCAUCGUGGCCUUCCTT-B	-3'
A	3'-	L-T _S T UACUGGUAGCACCGGAAGG	-5'
		ANTISENSE STRAND (SEQ ID NO 799)	
		SENSE STRAND (SEQ ID NO 800)	j
	5'-	<u>augaccaucguggccuuccTsT</u>	-3'
B	√ 3'-	L-T _S Tu <u>a</u> cuggu <u>a</u> gc <u>a</u> ccgg <u>a</u> agg	-5'
		ANTISENSE STRAND (SEQ ID NO 801)	
		SENSE STRAND (SEQ ID NO 802)	
	5'-	B-AuGAccAucGuGGccuuccTT-B	-3'
C	₹ 3'-	L-T _S TuAcuGGuAGcAccGGAAGG	-5' }
		ANTISENSE STRAND (SEQ ID NO 803)	
		SENSE STRAND (SEQ ID NO 804)	7
		SENDE BIRTID (BEQ ED 110 001)	•
D		B-AuGAccAucGuGGccuuccTT-B	-3'
	3'-	$L-T_STu\underline{a}cuggu\underline{a}gc\underline{a}ccgg\underline{a}\underline{a}gg$	-5'
		ANTISENSE STRAND (SEQ ID NO 801)	
		SENSE STRAND (SEQ ID NO 805)	,
	5'-	B-AuGAccAucGuGGccuuccTT-B	-3'
E	₹ 3'-	L-T _S Tu <u>a</u> cuggu <u>a</u> gc <u>a</u> ccgg <u>aa</u> gg	-5' >
		ANTISENSE STRAND (SEQ ID NO 801)	
		SENSE STRAND (SEQ ID NO 804)	
	5'-	B-AuGAccAucGuGGccuuccTT-B	-3'
F	₹ 3'-	L-T _S TuAcuGGuAGcAccGGAAGG	-5' }
		ANTISENSE STRAND (SEQ ID NO 806)	
•	21.0	O Methyl or 2'-deoxy-2'-fluoro	J

lower case = 2'-O-Methyl or 2'-deoxy-2'-fluoro italic lower case = 2'-deoxy-2'-fluoro underline = 2'-O-methyl

ITALIC UPPER CASE = DEOXY

B = ABASIC, INVERTED ABASIC, INVERTED

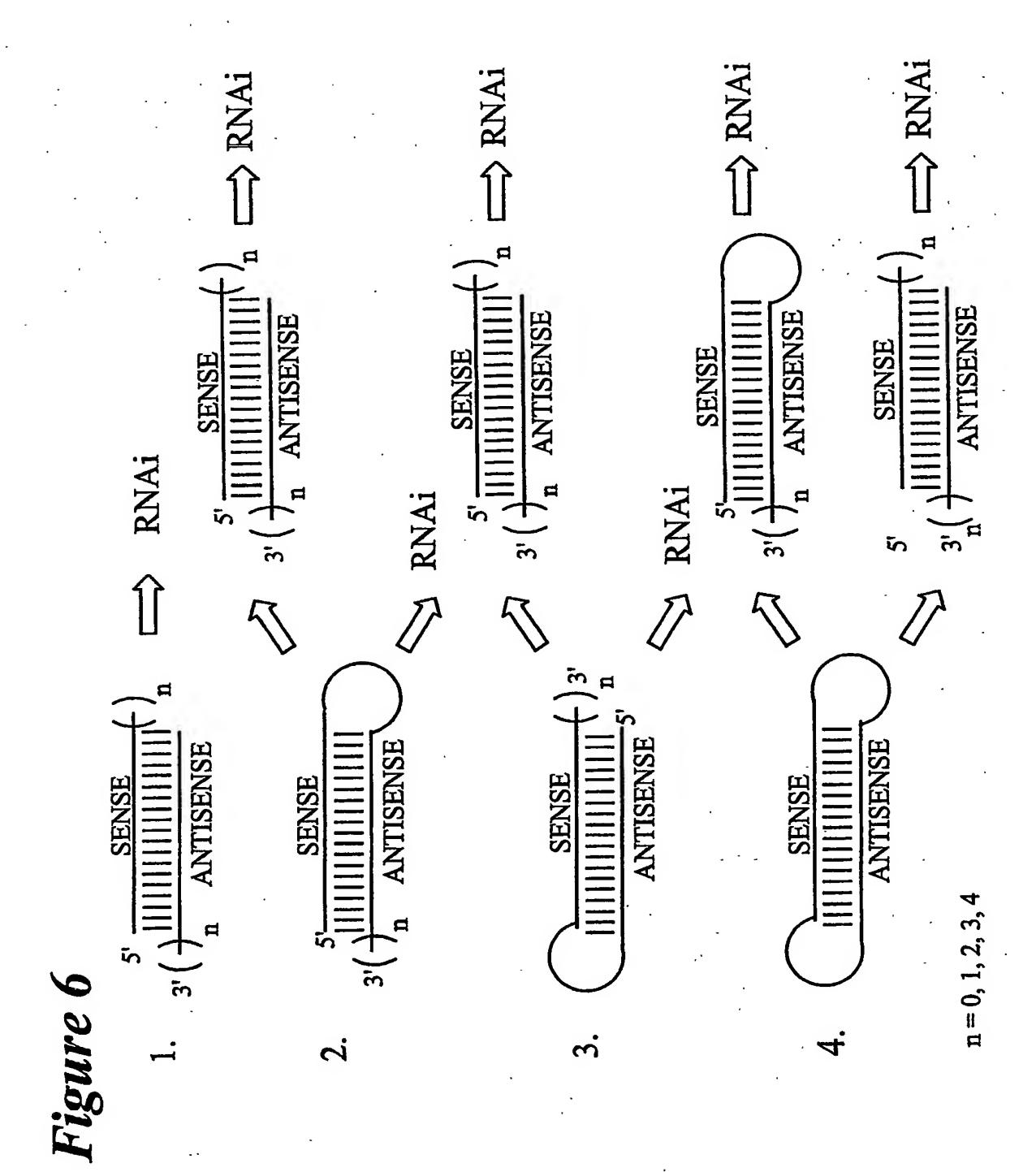
NUCLEOTIDE OR OTHER TERMINAL

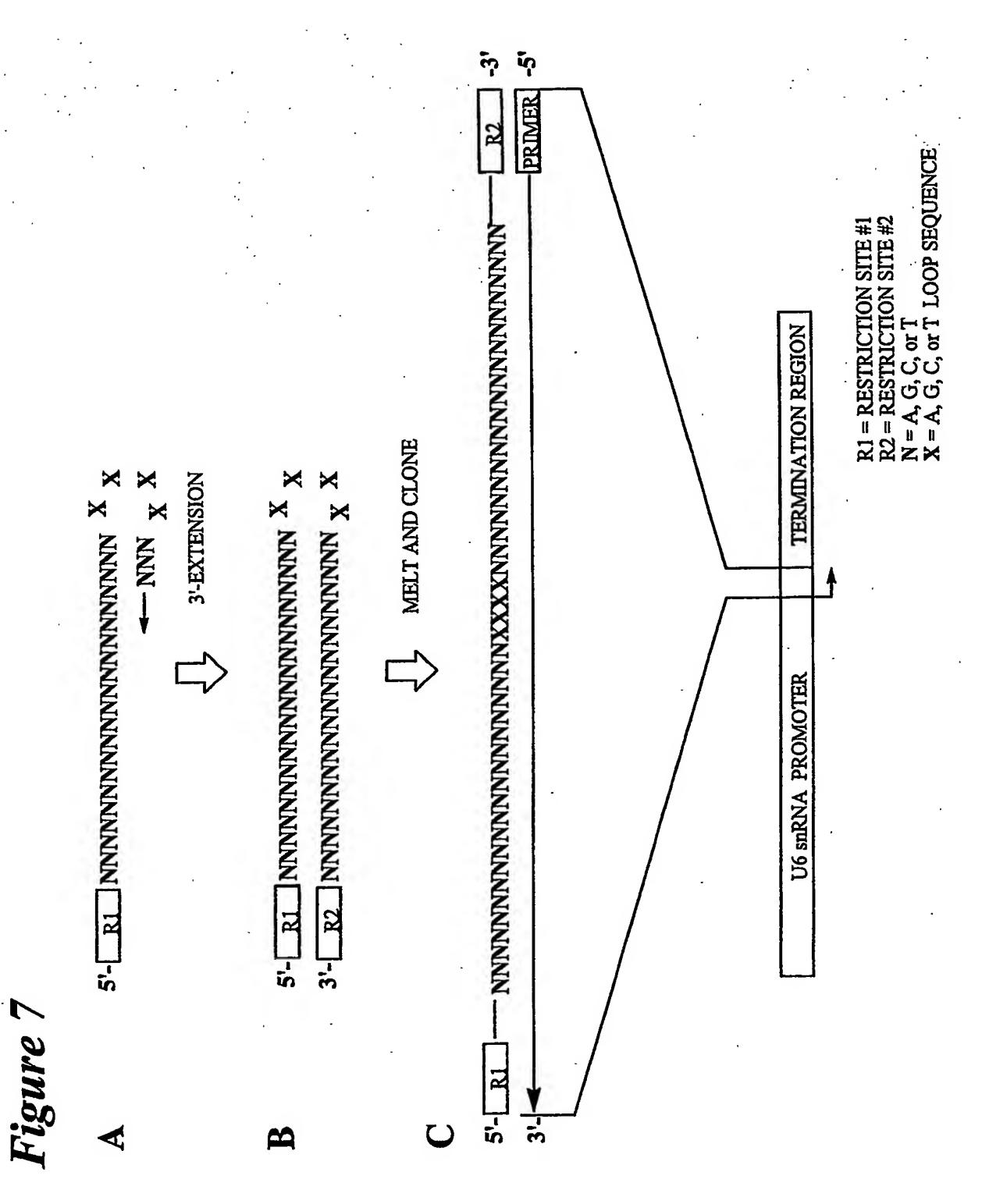
CAP THAT IS OPTIONALLY PRESENT

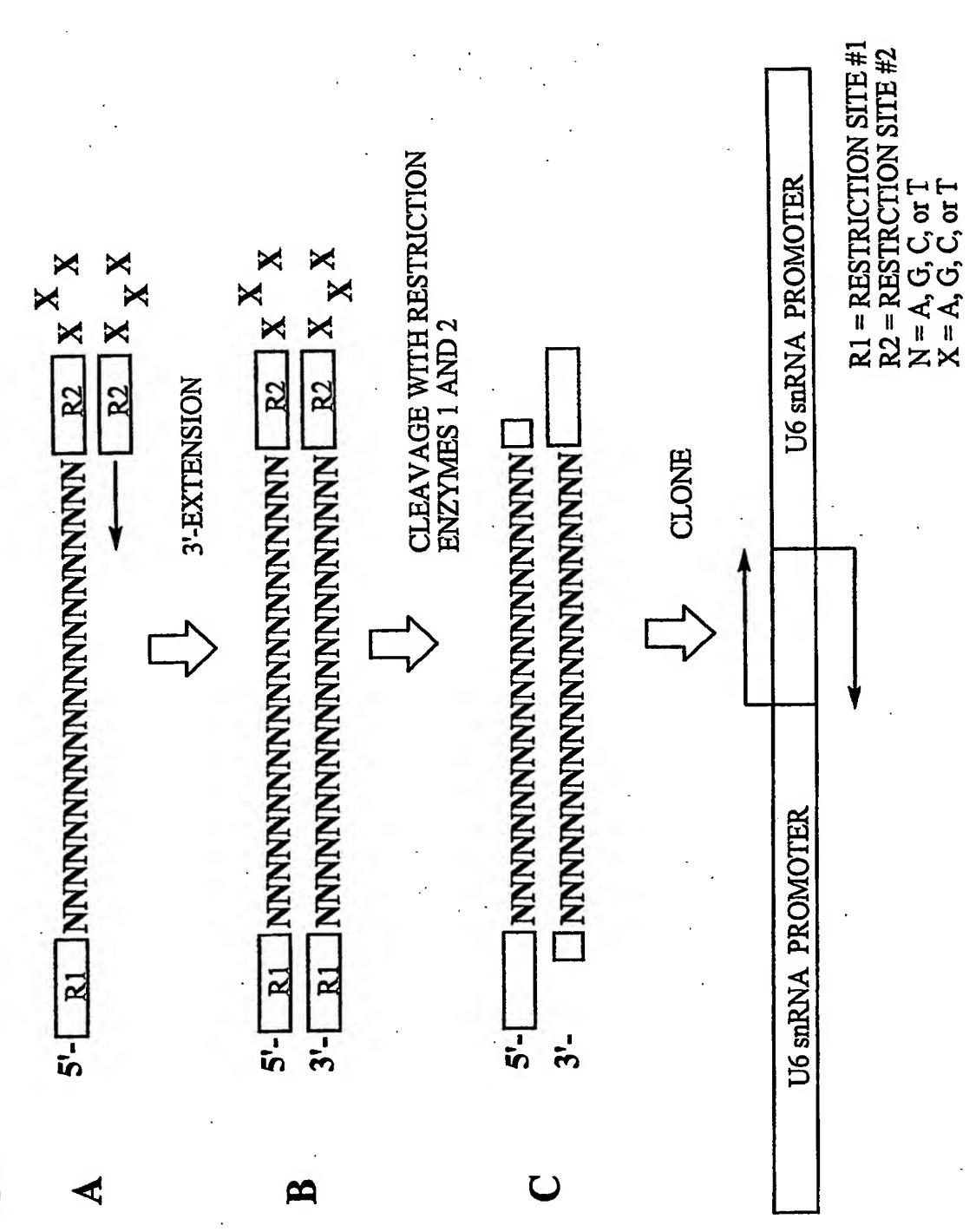
S = PHOSPHOROTHIOATE OR

PHOSPHORODITHIOATE OPTIONALLY PRESENT

L = GLYCERYL MOIETY or B OPTIONALLY PRESENT



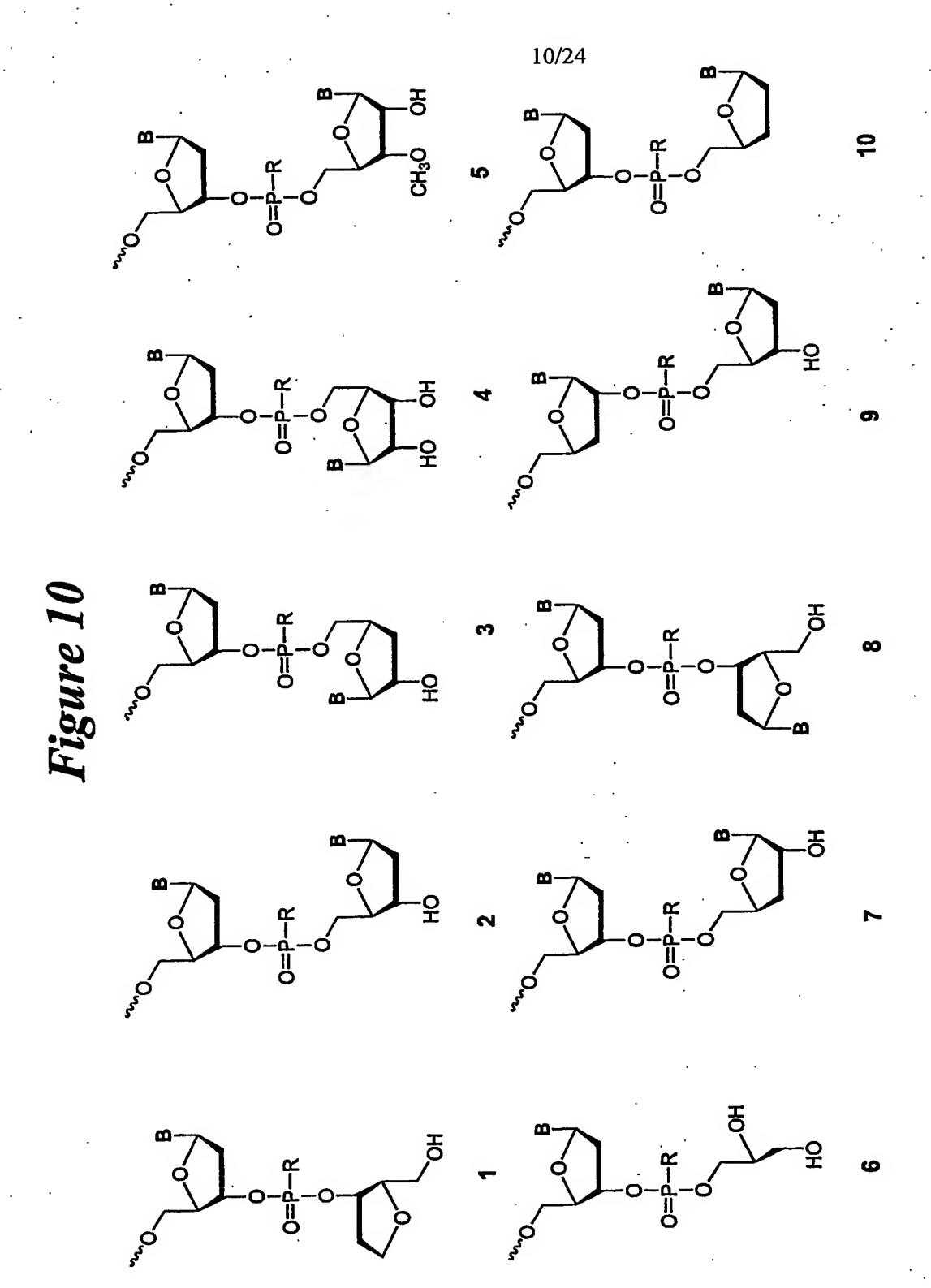




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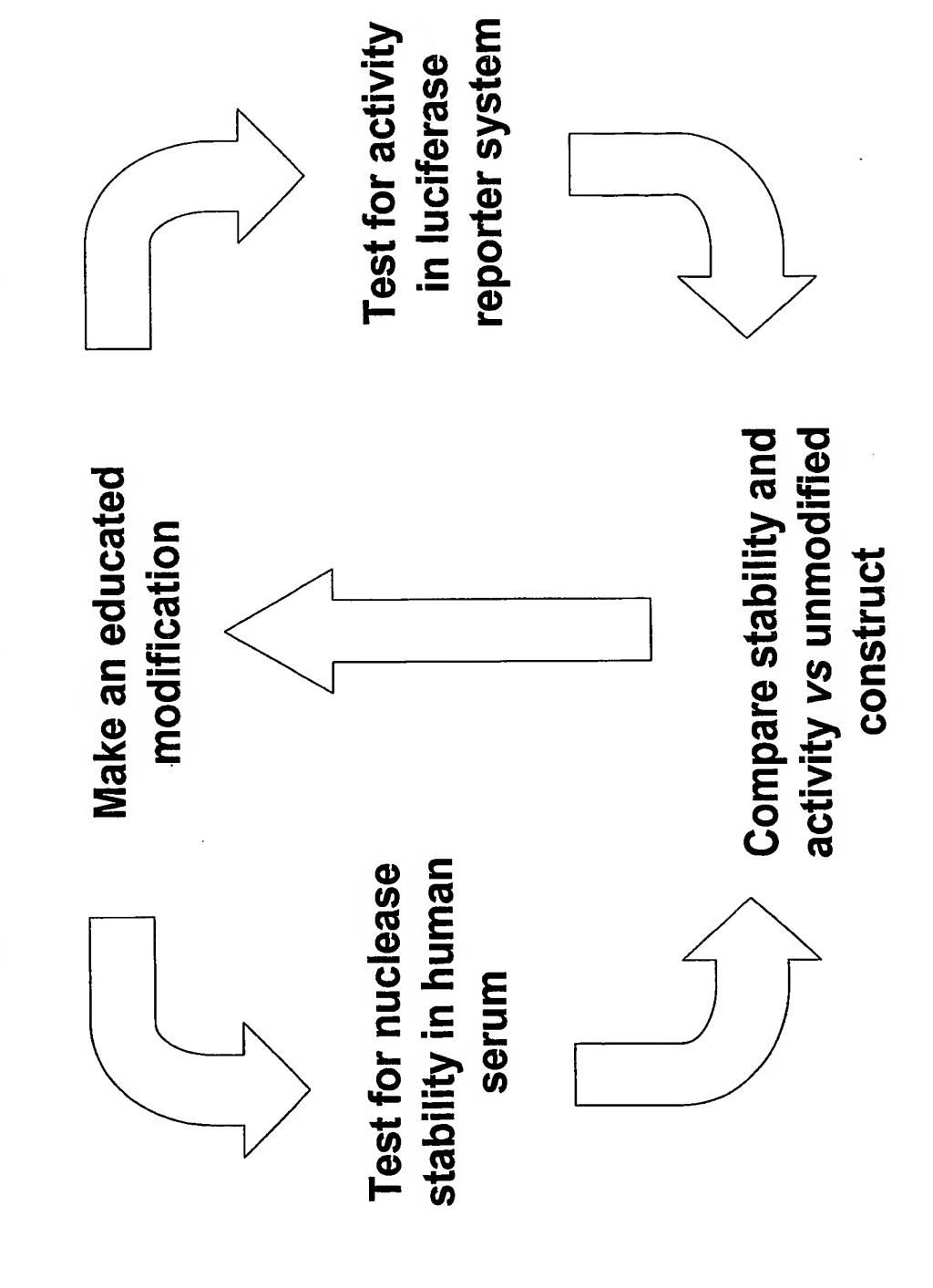
elect cells exhibiting desired phenotype Select

Transduce target cells



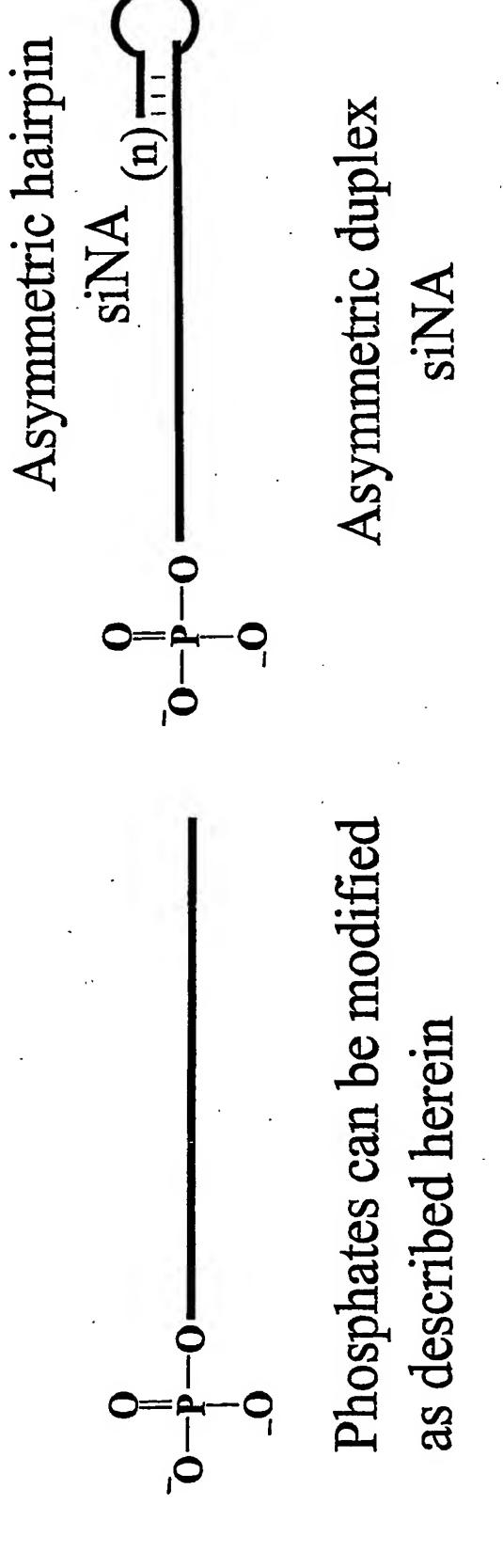
R = O, S, N, alkyl, substituted alkyl, O-alkyl, S-alkyl, alkaryl, or aralkyl B = Independently any nucleotide base, either naturally occurring or chemically modified, or optionally H (abasic)

Figure 11: Modification Strategy

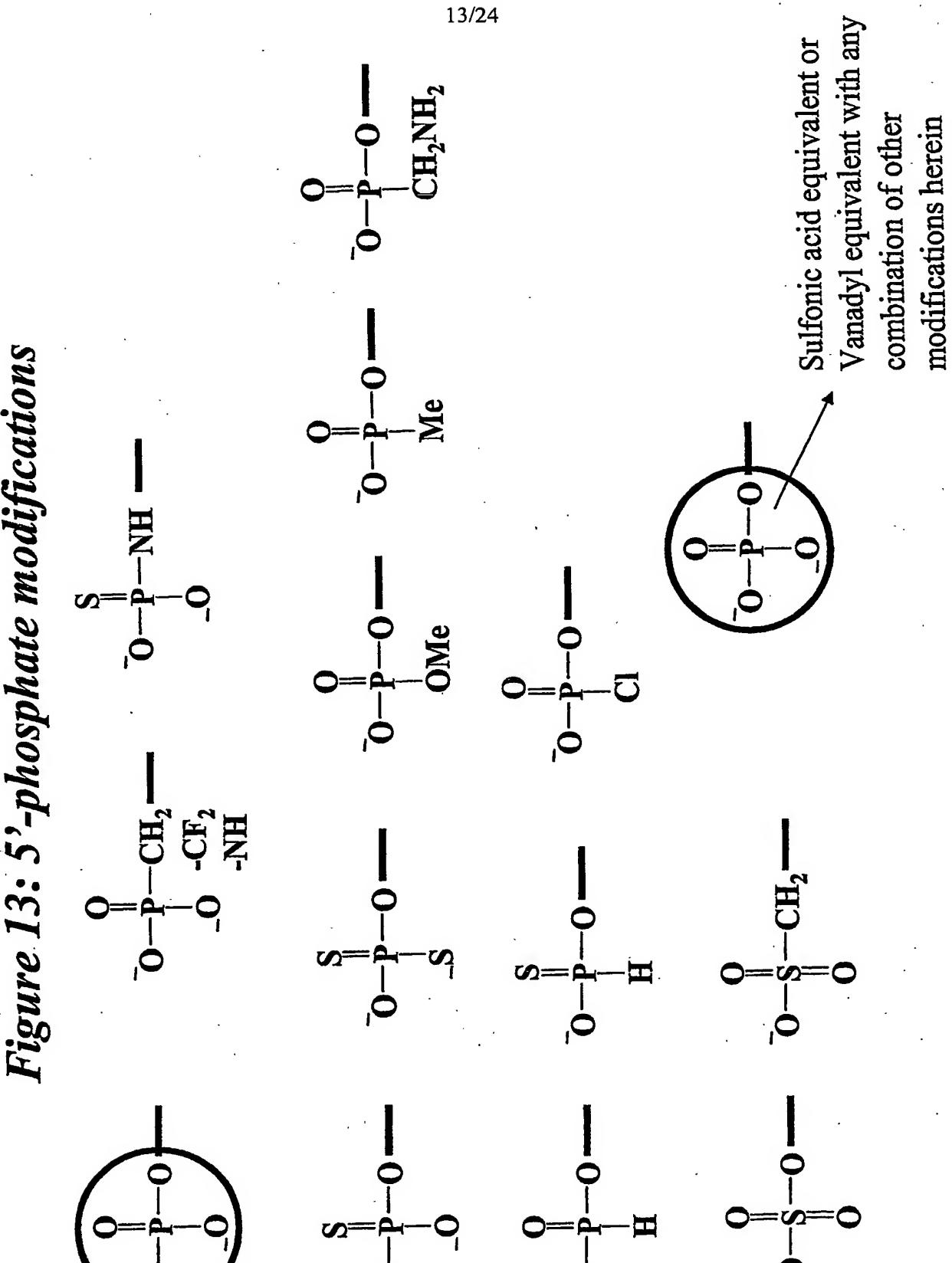


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Figure 12: Phosphorylated siNA construct



osphate modifications



oligonucleotide constructs that utilize Palindrome or repeat sequences Figure 14A: Duplex forming

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containing palindrome/repeat sequence Identify Target Nucleic Acid sequence (e.g., 14 to 24 nucleotides in length) at 5'-end (dashed portion)

Target Nucleic Acid sequence of (i) above Design Complementary Sequence to the

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(E)

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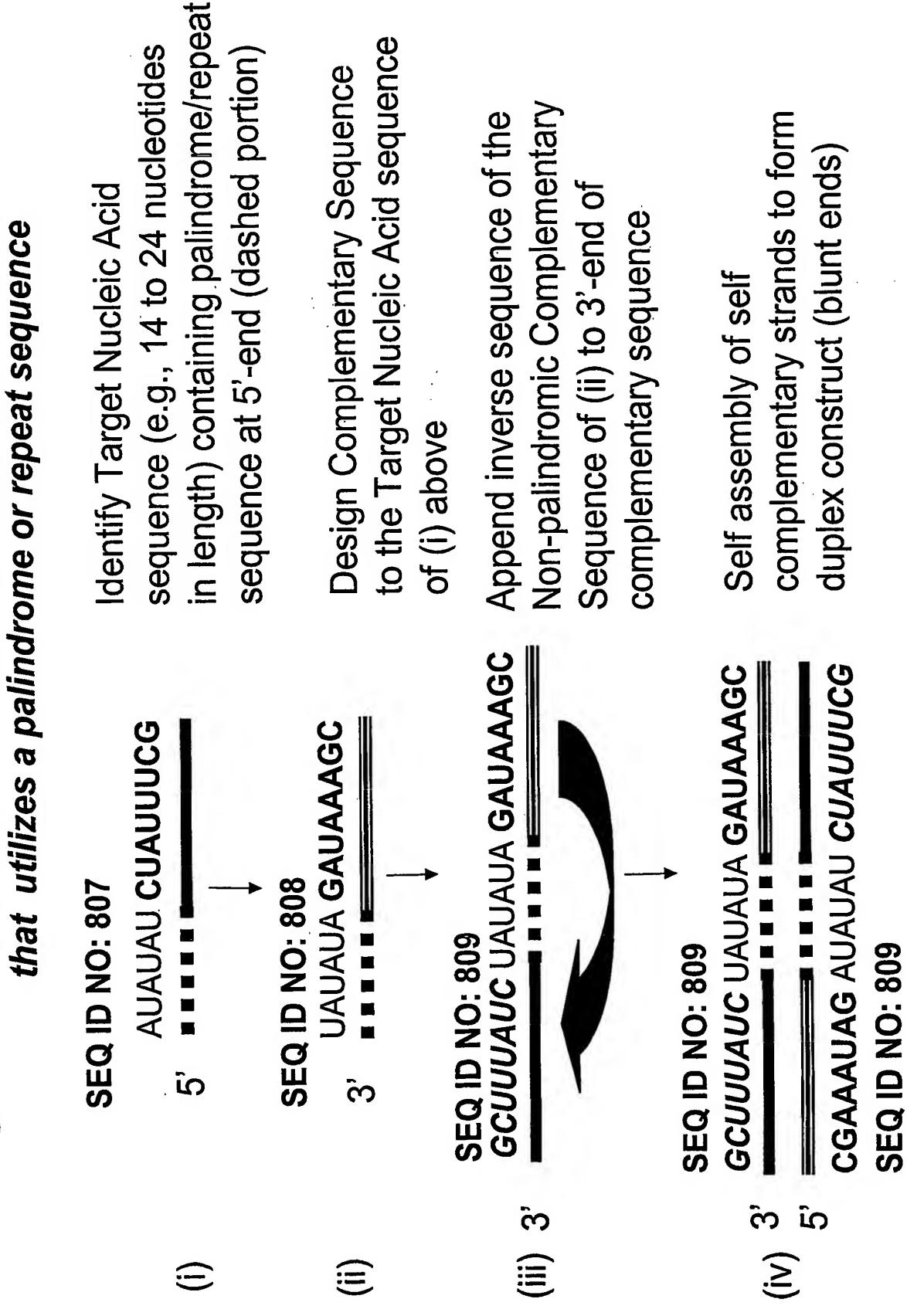
Sequence of (ii) to 3'-end of complementary Non-palindromic Complementary Append inverse sequence of the sednence

Self assembly of self complementary strands to form duplex construct

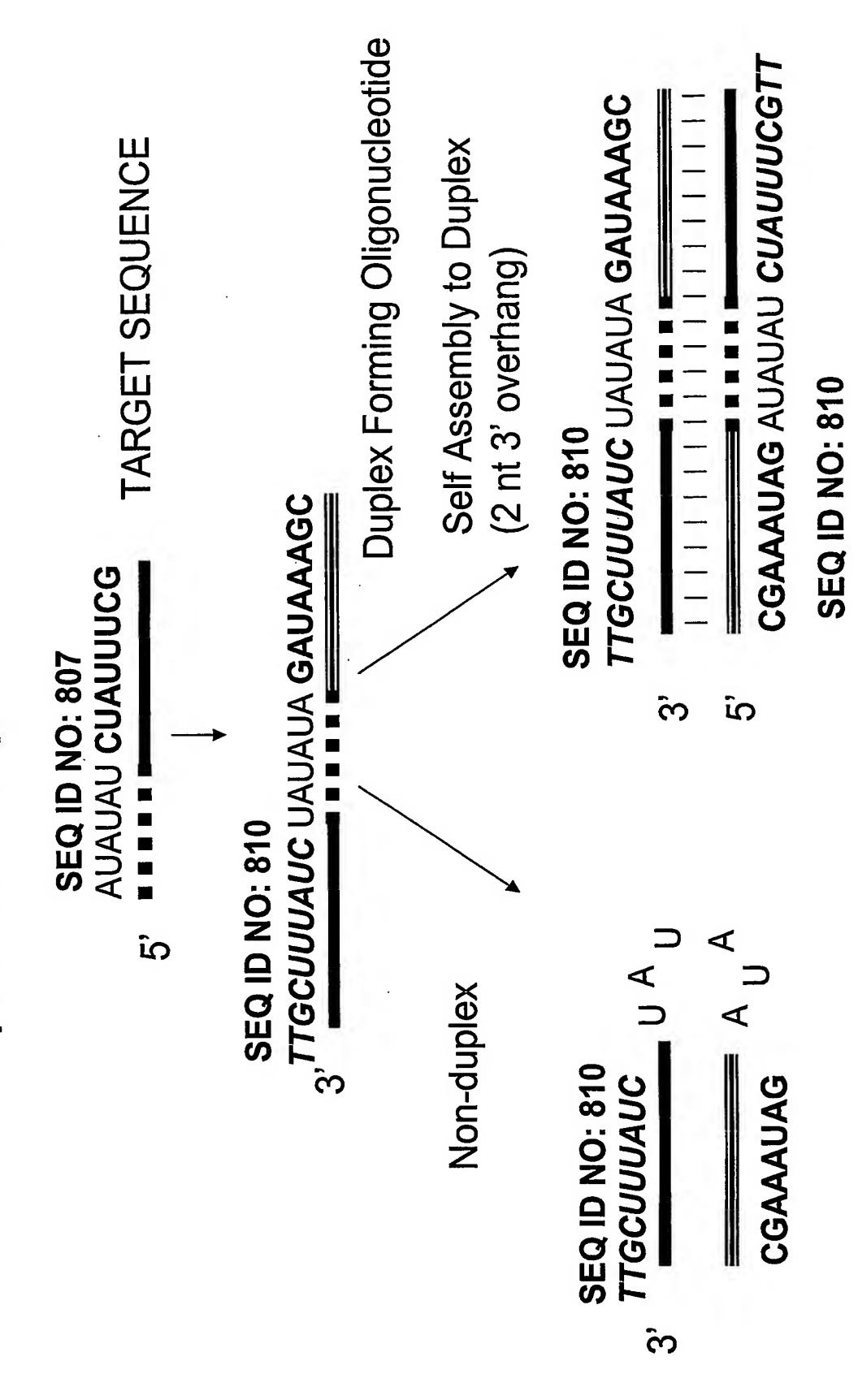
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(i)

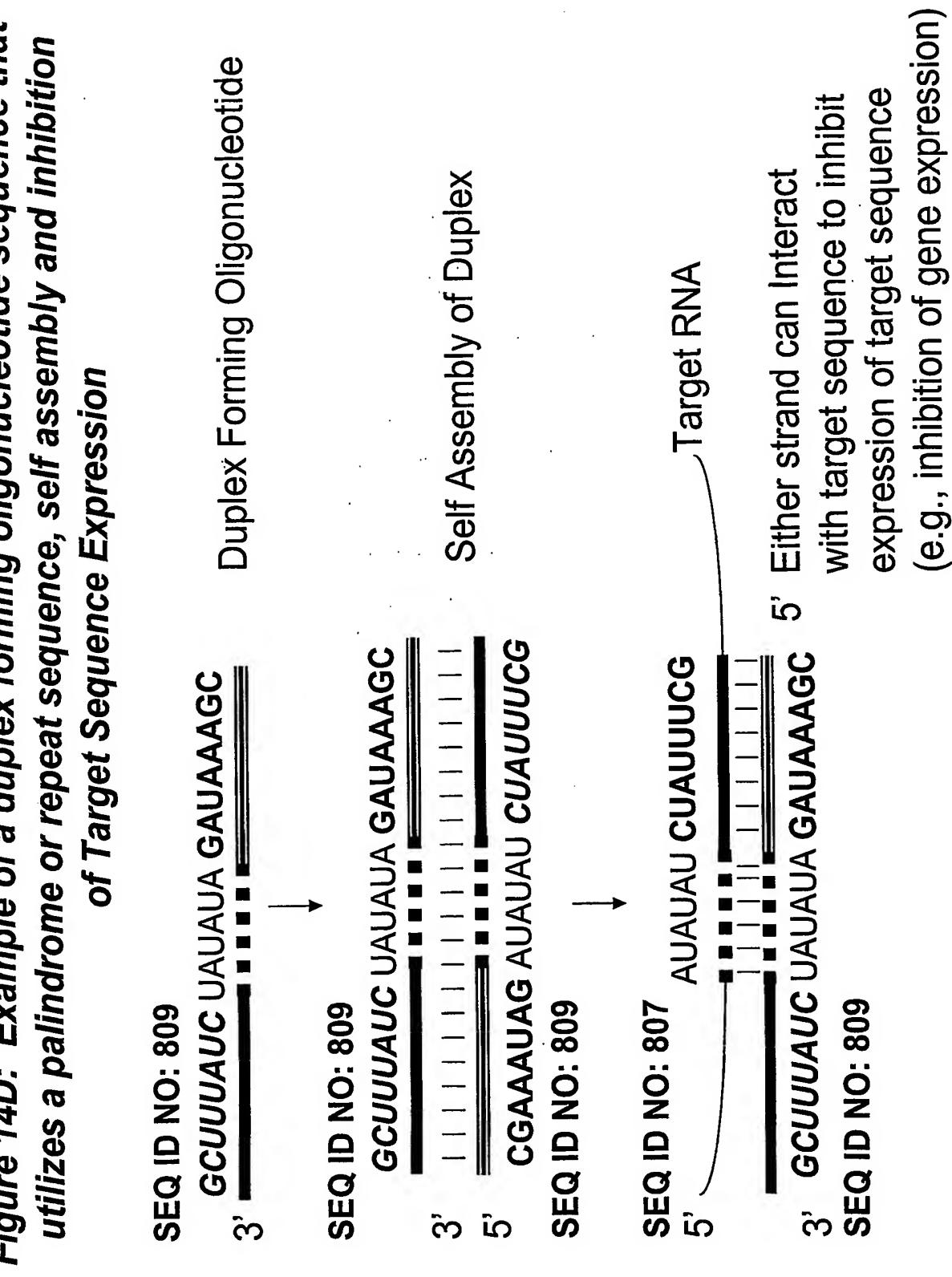
Figure 14B: Example of a duplex forming oligonucleotide sequence



forming oligonucleotide sequence that utilizes a palindrome or repeat sequence, self assembly Figure 14C: Example of a duplex



forming oligonucleotide sequence that utilizes a palindrome or repeat sequence, self assembly and inhibition Figure 14D: Example of a duplex



oligonucleotide constructs that utilize artificial palindrome or repeat sequences Figure 15: Duplex forming

Identify Target Nucleic Acid sequence (e.g., 14 to 24 nucleotides in length)

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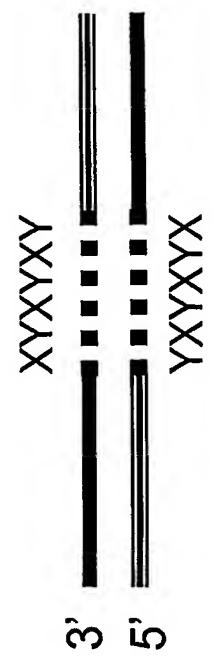
Design Complementary Sequence and utilize modified nucleotides (shown as X, Y) that interact with a portion of the target sequence and result in the formation of a palindrome/repeat sequence (e.g., 2 to 12 nucleotides) at 3'-end (dashed portion)

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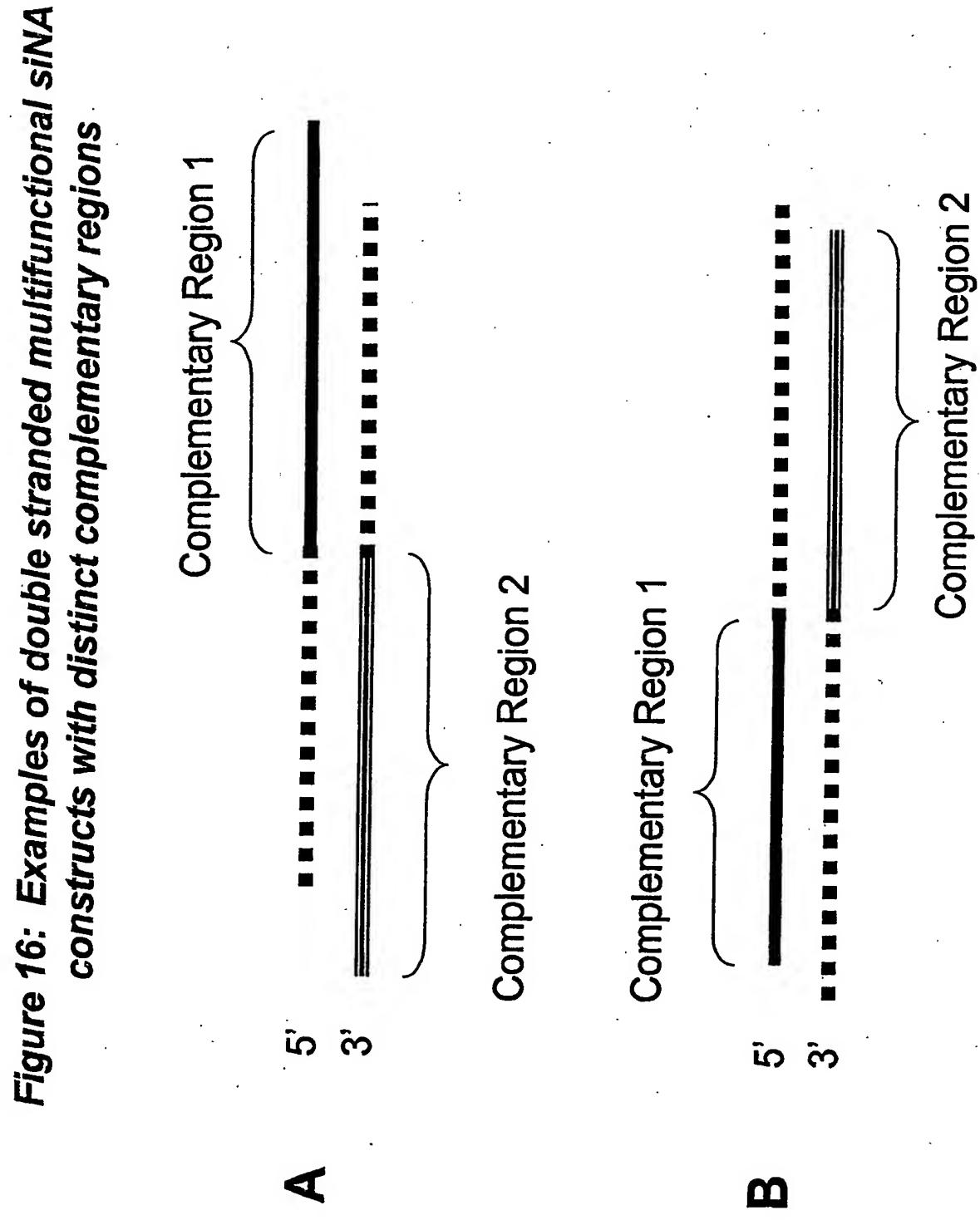
Append inverse sequence of Complementary region to 3'-end of palindrome/repeat sequence

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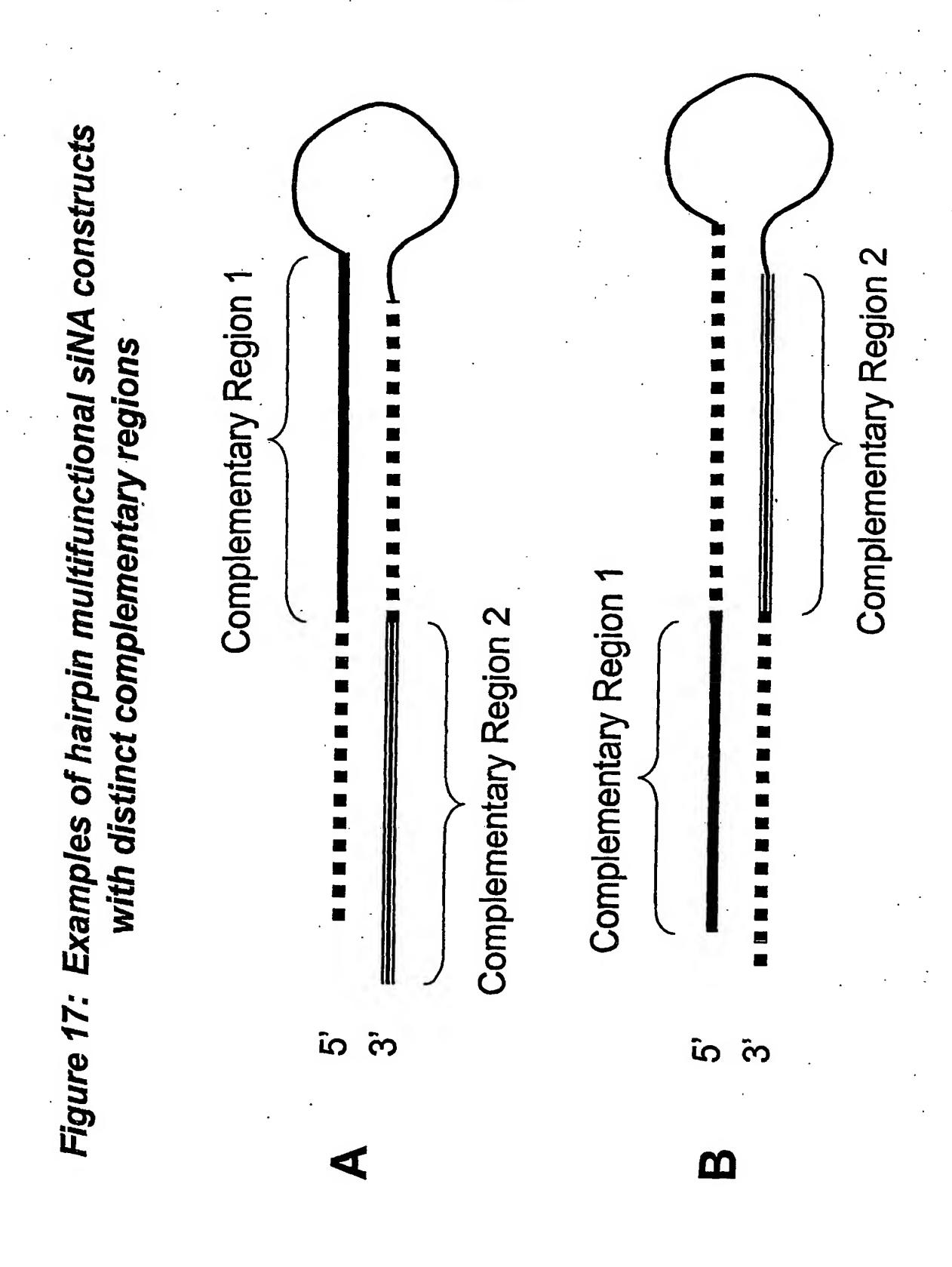
Hybridize self complementary strands to form duplex siNA construct



of double stranded multifunctional siNA Figure 16: Examples



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and a self complementary/palindrome region Figure 18: Examples of double stranded multifunctional siNA constructs with distinct complementary regions

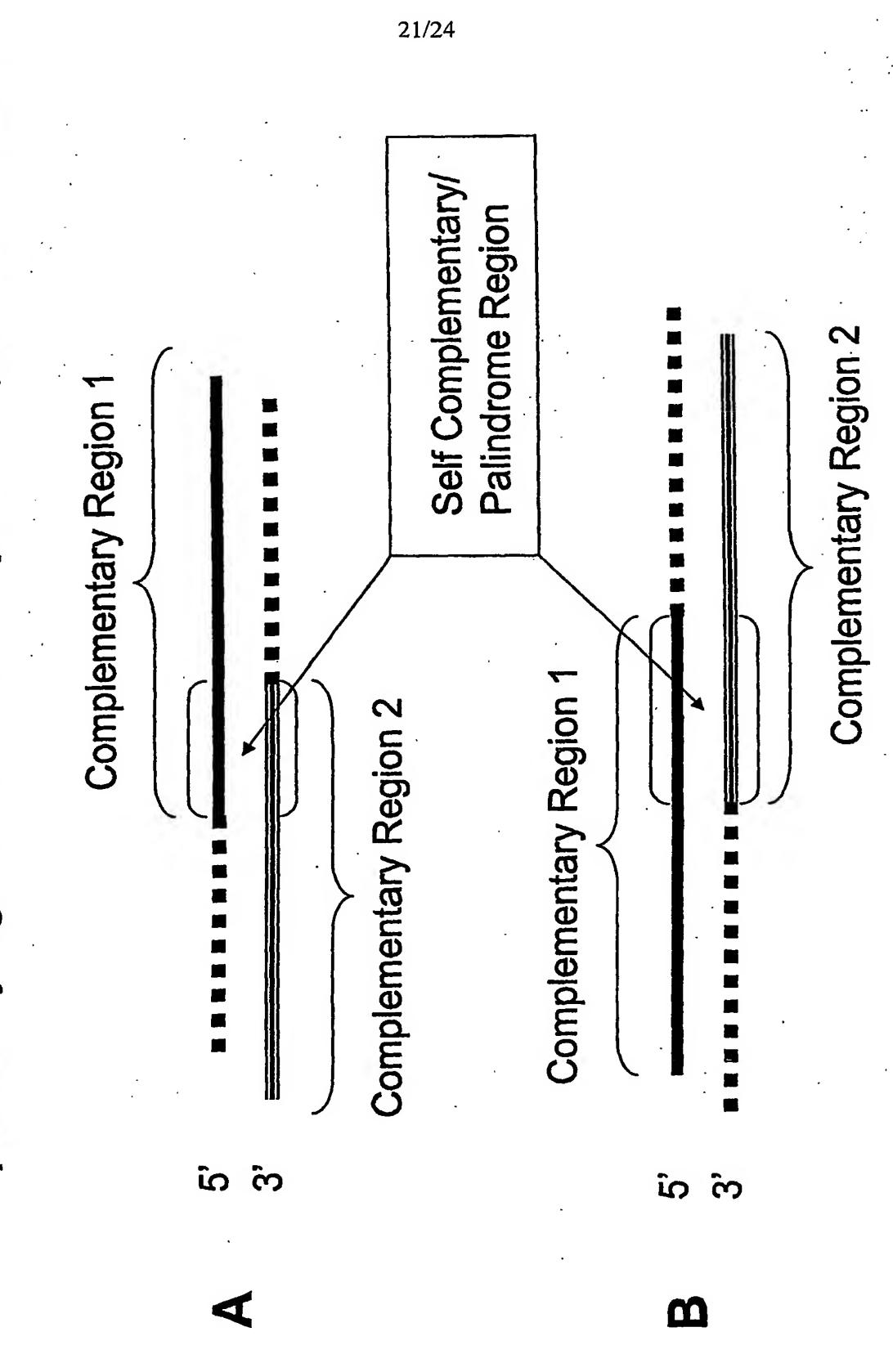


Figure 19: Examples of hair, distinct complementary regions

